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ABSTRACT

Background. Vulvovaginal candidiasis (VVC) is a common cause of vulvovaginal itching and discharge. This article discusses the latest CDC STI Treatment Guidelines for VVC.

Methods. A literature search of relevant topics was performed, and a team of experts was convened to discuss (1) diagnosis/testing modalities; treatment of (2) uncomplicated VVC , (3) complicated VVC, and (4) VVC caused by non-*albicans* yeast; (5) alternative treatment regimens; (6) susceptibility testing of yeast; Special Populations: (7) pregnancy and (8) HIV and VVC.

Results. Yeast culture remains the gold standard for diagnoses. Newer molecular assays have been developed for the diagnosis of VVC and perform well. Azole antifungals remain the treatment of choice for uncomplicated VVC. Two new drugs, TOL-463 and recently FDA-approved ibrexafungerp, appeared promising in clinical trials. For recurrent VVC, oteseconazole, not yet commercially available, may represent a new option. For non-*albicans* yeast infections in symptomatic patients, boric acid appears useful. No evidence supports the use of alternative treatments, including probiotics. Fluconazole during pregnancy may be associated with spontaneous abortion and craniofacial and heart defects. In women with HIV infection, lower CD4+ T-cell counts are associated with increased rates of VVC, and

VVC is associated with increased viral shedding. Treatment measures in women with HIV infection are identical to those women without HIV infection.

Conclusions. There has been significant new knowledge generated about VVC since the 2015 CDC Guidelines which have led to changing recommendations.

INTRODUCTION

One of the most common causes of vulvovaginal itching and discharge worldwide, vulvovaginal candidiasis (VVC) is a condition characterized by yeast colonization, most frequently by *Candida albicans*. In the United States, VVC represents the second most common cause of vaginal infections, affecting 70-75% of women during their lifetime and resulting in an estimated 1.4 million outpatient visits each year [1,2]. At an annual treatment cost of at least $368 million for VVC [1] and lost productivity costs of over $4.8 billion for recurrent VVC alone [3], VVC represents a significant economic burden on the American healthcare system as well as a serious public health issue.

Although most women with vaginal yeast colonization are asymptomatic, many experience varying degrees of vaginal itching, the symptom most specific to VVC [2]. Some patients may also experience vaginal soreness, swelling, dyspareunia, dysuria, or increased discharge [2]. VVC may be diagnosed clinically, via microscopy, or with yeast culture, and the vast majority of cases are treated with azole antifungals [4].

Although much is known about the presentation, diagnosis, and management of VVC, knowledge continues to be generated. Thus periodic reviews of the literature are required to ensure that treatment guidelines reflect the most recent findings. To update the treatment guidelines for vulvovaginal candidiasis, a team of experts was convened to review the literature concerning several key topic areas: (1) data concerning diagnosis and testing modalities; (2) treatment of uncomplicated VVC; (3) treatment of complicated VVC; (4) VVC caused by non-

albicans yeast species; (5) alternative regimens for treatment of VVC; (6) susceptibility testing of yeast and its role in treatment; (7) pregnancy and VVC; and (8) HIV and VVC. This article serves as a supplement to the updated 2021 CDC STD treatment guidelines for vulvovaginal candidiasis and highlights clinically important findings relevant to the aforementioned key questions. Additionally, it poses areas for further research necessary for the continued development of our understanding of this common but complex condition.

METHODS

Using the PubMed database of the US National Library of Medicine, we conducted a search of the literature published between January 2013 and June 2019, restricting results to English-language articles concerning human subjects. To identify studies of interest, we used the following search and Medical Subject Heading (MeSH) terms: (candidiasis, vulvovaginal"[MeSH Terms] OR "candidiasis"[All Fields] AND "vulvovaginal"[All Fields]) OR "vulvovaginal candidiasis"[All Fields] OR ("yeast"[All Fields] AND "vaginitis"[All Fields]) OR "yeast vaginitis"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]). Given the complexities associated with diagnosing and treating *C. glabrata*, we additionally searched for studies concerning this species: ("candida glabrata"[MeSH Terms] OR ("candida"[All Fields] AND "glabrata"[All Fields]) OR "candida glabrata"[All Fields]) AND ("vaginitis"[MeSH Terms] OR "vaginitis"[All Fields]). Additionally, we searched for articles addressing VVC and pregnancy:

("vaginitis"[MeSH Terms] OR "vaginitis"[All Fields]) AND ("yeasts"[MeSH Terms] OR "yeasts"[All Fields] OR "yeast"[All Fields] OR "saccharomyces cerevisiae"[MeSH Terms] OR ("saccharomyces"[All Fields] AND "cerevisiae"[All Fields]) OR "saccharomyces cerevisiae"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]). Lastly, we searched for studies concerning both VVC and HIV: ("candidiasis, vulvovaginal"[MeSH Terms] OR ("candidiasis"[All Fields] AND "vulvovaginal"[All Fields]) OR "vulvovaginal candidiasis"[All Fields] OR ("vulvovaginal"[All Fields] AND "candidiasis"[All Fields])) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields] OR "hiv seropositivity"[MeSH Terms] OR ("hiv"[All Fields] AND "seropositivity"[All Fields]) OR "hiv seropositivity"[All Fields]). A total of 816 manuscripts were identified and screened, 70 selected for review, and ultimately 45 were included in the qualitative synthesis for the panel consideration.

Using online searches of pharmacies, phone calls to pharmacies, and physical visits to pharmacies, we reviewed the availability of the regimens suggested by the 2015 treatment guidelines (Table 2).

RESULTS

Diagnosis of Vulvovaginal Candidiasis

Although microscopy and clinical suspicion have been used to diagnose VVC for decades, culture has remained the gold standard for diagnosis of vaginal fungal infections. While valuable tools, all three diagnostic methods have drawbacks. Both microscopy and clinical diagnosis have poor sensitivity, while yeast cultures can lead to a delay in diagnosis and treatment. Culture of most *Candida* species takes a

minimum of 48-72 hours, precluding early treatment for the approximately 50% of infected patients with negative microscopy. Given this delay, many providers rely on microscopy or clinical diagnosis for patients presenting with symptoms consistent with VVC. This approach may result in misdiagnosis and unnecessary treatment. In fact, less than half of patients who are treated for VVC are diagnosed with an objective assay [5].

Given the limitations of current methods of VVC diagnosis and the growing popularity of molecular testing for the STI diagnosis, a growing number of commercial laboratories have developed molecular tests for VVC. Until recently, the performance characteristics of molecular testing for VVC were unknown. In a multi-site prospective cohort study, PCR for the Candida group (*C. albicans*, *C. dubliniensis*, *C. parapsilosis*, and *C. tropicalis*) was found to have high clinical accuracy (sensitivity 90.9%, specificity 94.1%, PPV 87.8%, and NPV 95.7%) [6]. Sensitivity was lower for *C. glabrata* (75.9%) but specificity, PPV, and NPV remained high for this species (99.7%, 81.6%, and 99.6% respectively). A later study of this same population compared real-time PCR to clinical microscopy and found that for the *Candida* group, PCR yielded higher sensitivity (90.7% vs. 57.5%), specificity (93.6% vs. 89.4%), PPV (87.2% vs. 72.2%) and NPV (95.5% vs. 81.4%) than clinical diagnosis [7]. Clinicians should be aware that some commercially available PCR tests for yeast are not FDA-cleared and have not published their performance characteristics. Thus, providers who choose PCR methods to diagnose VVC should be familiar with the performance characteristics. In general, molecular diagnostic methods appear promising and may replace culture as the gold standard in the future. However,

even FDA-cleared tests may miss less common species of yeasts that infrequently cause VVC. Unlike culture, PCR does not make the organism available for susceptibility testing.

Treatment of Vulvovaginal Candidiasis

VVC can be classified as either uncomplicated or complicated (Table 1) depending on factors including infection severity, yeast species, and immune system integrity [1]. In general, complicated VVC is less likely to respond to treatment and requires more aggressive regimens to completely resolve. Given the significant prognostic differences between uncomplicated and complicated VVC, the differentiation between these two conditions is necessary.

Treatment of Uncomplicated Vulvovaginal Candidiasis

Azole antifungals continue to be the backbone of VVC treatment and are adequate to completely resolve candida infections in most cases of uncomplicated VVC. These medications come in a variety of formulations and can be administered orally or topically as vaginal creams, ointments, or suppositories. Our search of available regimens for the treatment of VVC found that, to date, none of the recommended medications have been removed from the market, and no additional formulations have been introduced. As such, the recommended treatment of uncomplicated VVC remains unchanged.

Recently approved is the oral antifungal agent ibrexafungerp (formerly SCY-078), a semi-synthetic triterpenoid antifungal glucan synthase inhibitor which

affects cell wall metabolism. In a small randomized controlled trial, subjects with moderate to severe VVC were treated with 3 or 5 days of either ibrexafungerp or 150mg oral fluconazole. Those on the ibrexafungerp regimens had numerically higher clinical (78.1% vs. 65.6%) and mycological (70.3% vs. 68.8%) cure rates and identical therapeutic cure rates (56.3%) at 24 days post-treatment [8]. At 120 days post-treatment, the ibrexafungerp regimens continued to perform well, with clinical cure rates of 88% compared to 65% in the fluconazole arm. Additionally, the recurrence rate at 120 days was lower for the ibrexafungerp groups than the fluconazole group (4% vs. 15%) [8]. This drug may end up being particularly useful for azole intolerant or resistant VVC.

In development is TOL-463, a novel boric acid-based vaginal anti-infective enhanced with ethylenediaminetetraacetic acid (EDTA). In a small phase 2 randomized controlled trial of women with either VVC, bacterial vaginosis (BV) or both, participants were assigned to take TOL-463 as either a vaginal gel or an insert. In the women with VVC, the insert showed higher rates of cure than the gel (92% vs. 81% clinical cure rate, 85% vs. 81% mycological cure rate). Both methods were found to be effective and safe [9], but without evidence of superiority over available antifungal therapies.

For both of these medications, further research is needed to determine the role they will ultimately play in treating VVC.

Treatment of Recurrent Vulvovaginal Candidiasis

Recurrent VVC (RVVC) is defined as three or more symptomatic episodes of VVC over 12 months [10]. In the past, RVVC was defined as four or more episodes

over 12 months, but current treatment protocols, whose synopses can be reviewed on clinicaltrials.gov, confirm that three or more has become the accepted case definition. Usually thought to affect a small proportion of women (<5%), a recent internet survey of more than 6000 women from five European countries and the United States found the prevalence of self-reported RVVC to be 9%, with the highest prevalence in women 25 to 34 years old (12%)[11]. Although self-report is prone to bias, this study suggests that RVVC is more common than traditionally thought, especially among young women, and that additional studies of its prevalence that use validated methods of diagnosing VVC are warranted and necessary. RVVC is associated with significant morbidity. In addition to the itching, burning, swelling, and discomfort often associated with VVC, women with recurrent VVC often also suffer from low self-esteem, loss of confidence, challenges participating in their regular interests, and difficulty in their sexual and intimate life [3]. Missed days of work and the resultant economic burden compound these issues, contributing to a cycle of stress and anxiety. In the United States, recurrent VVC is estimated to affect 6 million women, causing approximately $4.7 billion in lost productivity annually [3].

Little is known about host factors that contribute to RVVC in women; possible factors include genetic predisposition in cases of idiopathic RVVC, as well as drug resistance or under-dosing. A recent retrospective study to assess differences in *in vivo* antifungal potency used the first positive yeast cultures from more than 200 women with recurrent VVC. The efficacy of six antifungals (fluconazole, itraconazole, miconazole, clotrimazole, terconazole, and nystatin)

against various yeast species was tested at both pH 4 (normal vaginal pH) and pH 7 (commonly used by labs when doing susceptibility testing). All medications tested were found to have higher minimum inhibitory concentrations (MICs) at pH 4 than at pH 7 [12]. The impact of pH differed by antifungal agent and yeast species, with the most significant difference in MIC was seen when terconazole was used to treat *C. glabrata*. In these cases, the MIC was more than 388-fold higher at pH 4 than at pH 7. The reduced susceptibility of *C. glabrata* at low pH confirms the findings of a previous study [13], and suggests that the activity of antifungal drugs should be tested at a vaginal pH of 4 rather than the laboratory standard of pH 7 as there may be clinically relevant and unrecognized azole drug resistance that may contribute to recurrence of VVC.

Maintenance fluconazole, the first line treatment for RVVC, has been shown to improve quality of life in 96% of women [14]; it is, however, uncommonly curative and recurrence occurs more frequently than was previously thought, with one study finding that more than 63% of women who had completed maintenance therapy continued to have ongoing infections [15]. For all of these reasons, recurrent VVC represents a significant public health issue in need of new treatment approaches.

In terms of treatment, oteseconazole (formerly known as VT-1161) is a promising, novel oral highly-selective inhibitor of fungal lanosterol demethylase (CYP51) medication which has a very long plasma half-life. In a double blind placebo-controlled randomized controlled trial of women with RVVC, patients treated with VT-1161 at either a high or low dose for 12 or 24 weeks showed

remarkably lower rates of recurrence than those on placebo at the 48 week study time point (4% vs. 52%) [16]. Analysis of phase 3 trials is expected to be available soon.

A novel approach to treating RVVC, a vaccine targeting a hyphal virulence factor of *Candida albicans*, has also been evaluated for the treatment of RVVC [17]. Clinical data has shown it to be safe, immunogenic, and capable of reducing the frequency of symptomatic VVC for up to 12 months, but only in a subset of women under 40 years of age.

Unlike treatment of urinary tract or bloodstream infections where susceptibility testing is routine for determining the best treatment, susceptibility testing for yeast infections has not been widely used. With growing concerns about resistance of both *albicans* and non-*albicans Candida*, susceptibility testing may help guide therapeutic choice, particularly at a pH of 4.0 which mimics the vaginal environment in premenopausal women with VVC. Susceptibility testing is most valuable in patients with VVC refractory to treatment (e.g. still symptomatic with a positive culture immediately after treatment).

Treatment of VVC caused by non-albicans Candida

Candida albicans is the species most commonly found to be causative of VVC. Vulvovaginal yeast infections can also be caused by non-*albicans* yeast including other species of *Candida* or even yeast used in baking, like *Saccharomyces cerevisiae* [18]. These other species can be more challenging to diagnose and treat; as such these women meet the diagnostic criteria for complicated VVC.

Evidence suggests that at least 50% of women colonized with non-a*lbicans* candida species experience minimal or no symptoms of VVC [19]. Relatively few studies have investigated clinical outcomes in non-*albicans* cases [20-23]. Since the last published guidelines, a retrospective analysis of non-*albicans* cases at a tertiary care center [24] found that yeast seemed to be responsible for symptoms in 29/55 cases of *C. glabrata*, 16/24 cases of *C. parapsilosis*, 4/7 cases of *C. tropicalis*, 3/5 cases of *C. lusitaniae* and 2/2 cases of *C. krusei*. In total, non-*albicans* yeast accounted for symptoms in 55.7% of the 97 investigated cases. The same study found that a majority of non-*albicans* VVC can be effectively treated with either fluconazole or boric acid. Fluconazole resulted in a mycologic cure in 81% of *C. parapsilosis* cases and 60% of *C. glabrata* cases, while an initial 21-30 day course of boric acid effected a cure in 75% of *C. parapsilosis* cases, 78% of *C. glabrata* cases, 100% of *C. tropicalis* cases, 80% of *C. lusitaniae* cases, and 100% of *C. krusei* cases [24].

Of 49 *C. parapsilosis* cases at another tertiary care center, 60% were symptomatic [25]. Of those symptomatic cases, the clinician felt that 65% were symptomatic due to colonization with *C. parapsilosis*. Although the dose and duration was not specified in this study, treatment with boric acid was reported as effective in all treated cases, while only 70% of isolates were susceptible to fluconazole. Given the challenges associated with treating non-*albicans* yeast because of drug resistance and the low virulence of many of these species of yeast, women who are found to be asymptomatically colonized should forgo drug treatment.

Alternative Treatments

Many women who suffer from VVC, especially recurrent VVC, turn to alternative treatments. The growing public interest and investment in alternative treatment regimens for treating VVC necessitates a review of the efficacy of these modalities.

Since the last update to the treatment guidelines for VVC, several international studies investigated alternative treatments, including the use of honey-based ointments and gels, combined ginger-clotrimazole vaginal cream, and essential oils including tea tree, laurel, anise, basil, bergamot, lavender, mint, oregano, grapefruit, rosemary, winter savory, and ginger [26-29]. Although some of these interventions had beneficial impacts such as reducing discharge or partial reduction of symptoms, in general they were equal or inferior to prescribed medications. Given the lack of regulation of these treatments and their associated vehicles, as well as the availability of FDA-approved alternatives that show higher rates of cure, we do not recommend their use for the treatment of VVC.

In addition to increasing popularity of herbal alternative treatments, there has been a surge in the popularity of probiotics in recent years, especially for the treatment of digestive and vaginal health issues. Between 2007 and 2012, the number of adults in the US taking probiotics or prebiotics quadrupled [30], and in 2017, American consumers spent $2 billion on probiotic supplements [31]. Several international groups have investigated the use of oral or vaginal probiotics for treatment or prophylaxis against VVC. Studies from Italy, Iran, Sweden, and Canada examined the impact of probiotics including *Lactobacillus fermentum, L. acidophilus,*

L. plantarum, L. rhamnosus, L. reuteri, L. gasseri, Bifidobacterium bifidum, and *B. longum* [32-36]. All of these studies suffered from methodological issues. As such, the use of alternative treatments including essential oils and oral or vaginal probiotics is not recommended for the treatment of VVC.

Special Populations

Pregnancy

Pregnancy is a known risk factor for VVC, likely due to pregnancy-related factors including increased estrogen levels, increased vaginal glycogen, and alterations in the immune system [37]. Given the risk of teratogenesis during this vulnerable period, all medications must be thoroughly studied before they are recommended for use during pregnancy.

A systematic review of congenital malformations and fluconazole use during the first trimester found a potential association between fluconazole and overall malformations (OR 1.10, 95% CI 0.98–1.25), heart defects (OR 1.29, 95% CI 1.05–1.58), and craniofacial defects (OR 1.25, 95% CI 0.88–1.77). The increased rates of overall malformations and craniofacial defects failed to meet significance [38]. The link between fluconazole use during pregnancy and the risk of craniofacial and cardiac defects was also seen in a case-control study from a database of more than 40,000 mothers and their newborns, which found significant epidemiologic associations between fluconazole use during pregnancy and cleft lip and/or palate (OR 5.53, 95% CI 1.68-18.24) as well as dextro-transposition of the great arteries (OR 7.56, 95% CI 1.22-35.45) [39].

Fluconazole use during pregnancy has also been associated with spontaneous abortion [40, 41], although no increased risk was seen if fluconazole use occurred in the year prior to pregnancy or if a topical azole was used [40]. Several studies with significant methodological flaws, primarily the use of microscopy instead of culture for diagnosis, demonstrated an association between VVC and preterm delivery [42-44]. Additional higher quality studies are needed to further investigate this relationship and to determine the degree of risk of preterm delivery among women with both symptomatic and asymptomatic yeast colonization. Current guidelines state that only topical azole therapy should be used to treat VVC in pregnancy.

HIV

Several international studies have evaluated the relationship between HIV infection and VVC. A retrospective cohort study from South Africa found that rates of VVC increased when CD4+ T cell counts were less than 200 cells/mm^3 and plasma HIV RNA load was greater than 10,000 copies/mL [45]. VVC was also associated with increased vaginal viral shedding. In contrast, women on combination ART were 4-fold less likely to develop VVC. Although no studies yielded robust findings, the link between worsening viral control and VVC is echoed in studies from Brazil, Namibia and the US [46-48]. The treatment guidelines for women with HIV infection and VVC remain unchanged.

Future Needs

Significant knowledge about VVC has been generated since the publication of the last update to the CDC Treatment Guidelines, but there is still much that remains unknown or that requires further investigation. Specifically, home self-tests that are accurate for yeast are one intervention that might decrease VVC-associated healthcare spending and would expedite treatment for many women. In the same vein, widely available validated molecular testing would expedite diagnosis of VVC and identification of the causative species, allowing for timely and targeted treatment of infections while decreasing rates of misdiagnosis.

A study of the clinical utility and cost effectiveness of the various diagnostic methods and susceptibility testing available is vital as healthcare costs continue to rise. Identifying the most effective clinical workup, including the role of *in vitro* susceptibility testing, for patients with either uncomplicated or complicated VVC is one way to maximize quality of care while also minimizing costs to the patient and to standardizing best practices among providers.

There is a growing need for treatment options for non-*albicans* yeast and *C. albicans* infections resistant to azole. Although vaginal boric acid and possibly nystatin have been very useful, the only other medication that reliably treats non-*albicans* yeast is a compounded cream containing flucytosine, which is prohibitively expensive for many patients. Additionally, effective medications that do more than simply control cases of recurrent VVC are still lacking from our current armamentarium. Use of ineffective medications in these patients runs the risk of increasing antifungal resistance, making complete eradication of their infection even more challenging. Better therapies must be developed to treat recurrent VVC.

Finally, further studies should be conducted concerning the larger implications of VVC on human health and disease. Like many other causes of vaginitis, VVC and its impact on patients is often trivialized. As a result, the role that is plays in other diseases, chronic or acute, has been at best largely glossed over, at worst completely ignored. This significant public health issues requires serious research and inquiry if it is to be combatted on the national and global scale.

Conflicts of Interest

Dr. Nyirjesy has received research support from Mycovia Pharmaceuticals, Curatek Pharmaceuticals, Scynexis, Inc. and Hologic; he has served as a consultant for Mycovia Pharmaceuticals, Lupin Pharmaceuticals, Hologic, Scynexis, Inc, Daré Bioscience, Inc and BD. Carolyn Brookhart and Dr. Lazenby have no conflicts of interest to report. Dr. Schwebke has received research funding and consulting fees from Mycovia, Toltec,Scynexis, BD Diagnostics, and Hologic. Dr. Sobel has served as a consultant to Mycovia Pharmaceuticals, Scynexis and Lupin Pharmaceuticals.

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Table 1. Classification of Vulvovaginal Candidiasis

Uncomplicated VVC

- Sporadic or infrequent VVC
  AND
- Mild-to-moderate VVC
  AND
- Likely to be *Candida albicans*
  AND
- Non-immunocompromised women

Complicated VVC

- Recurrent VVC
  OR
- Severe VVC
  OR
- Non-albicans candidiasis
  OR
- Women with diabetes, immunocompromising conditions (e.g., HIV infection), debilitation, or immunosuppressive therapy (e.g., corticosteroids)

Abbreviation: VVC = vulvovaginal candidiasis.

From Workowski KA et al; Centers for Disease Control and Prevention. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187

Table 2. Recommended Regimens for Treatment of Vulvovaginal Candidiasis

Regimen	**Dosing**
Over-the-Counter Intravaginal Agents:	
Clotrimazole 1% cream	5 g intravaginally daily for 7–14 days
Clotrimazole 2% cream	5 g intravaginally daily for 3 days
Miconazole 2% cream	5 g intravaginally daily for 7 days
Miconazole 4% cream	5 g intravaginally daily for 3 days
Miconazole 100 mg vaginal suppository	One suppository daily for 7 days
Miconazole 200 mg vaginal suppository	One suppository for 3 days
Miconazole 1,200 mg vaginal suppository	One suppository for 1 day
Tioconazole 6.5% ointment	5 g intravaginally in a single application
Prescription Intravaginal Agents:	
Butoconazole 2% cream (single dose bioadhesive product)	5 g intravaginally in a single application
Terconazole 0.4% cream	5 g intravaginally daily for 7 days
Terconazole 0.8% cream	5 g intravaginally daily for 3 days
Terconazole 80 mg vaginal suppository	One suppository daily for 3 days
Oral Agent:	
Fluconazole 150 gm	Single dose

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